Acute toxicity following analytically confirmed use of the novel psychoactive substance (NPS) methiopropamine. A report from the Identification Of Novel psychoActive substances (IONA) study.

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Abstract

Objective: Use of the New Psychoactive Substance (NPS) methiopropamine was first reported in 2011, but there are limited data on its acute toxicity. We report 11 patients presenting with analytically confirmed methiopropamine use.

Methods: Adults presenting to 26 hospitals in the UK with severe acute toxicity after suspected NPS use were recruited from March 2015 to April 2018. Clinical features were recorded and biological samples analysed using tandem mass-spectrometry.

Results: Methiopropamine was detected in 11 of 414 patients, with the last detection in August 2016. It was the only substance detected in one patient; other substances detected included other NPS in nine and conventional drugs of misuse in five. Common features included tachycardia (10/11), agitation (7/11), confusion (7/11), reduced level of consciousness (5/11), hallucinations (5/11) and a raised creatine kinase (7/11). Median length of hospital-stay was 17hours; ten were discharged without sequelae and one was transferred for in-patient psychiatric treatment.

Conclusions: Methiopropamine was only detected during 2015 and 2016; most patients had other drugs detected, particularly other NPS. Raised CK was common but it is not possible to determine the degree to which this and other features could be contributed to by co-use of other substances.

Introduction

Methiopropamine (MPA, 1-(thiophen-2-yl)-2-methylaminopropane) is a synthetic methamphetamine analogue in which the benzene ring is replaced with a thiophene ring (Figure 1). It was originally synthesised in 1942 and previous *in vitro* work has shown that it is a reuptake inhibitor at dopamine and norepinephrine transporters with less effect on serotonin transporters.[1, 2]

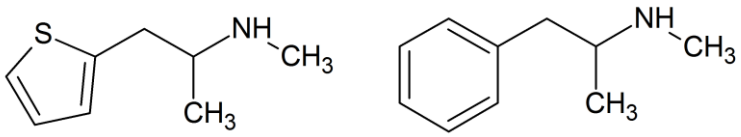

Figure 1. Chemical structure of Methiopropamine (left) compared to Methamphetamine (right).

Its use as a novel psychoactive substance (NPS) was first reported to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) in January 2011; by November 2016, methiopropamine use had been reported in 14 countries worldwide.[3-6] In the UK methiopropamine was subject to a Temporary Class Drug Order on 27th November 2015 and subsequently controlled as a Class-B substance under the Misuse of Drugs Act, 1971 on 27th November 2017.[7] By early 2018 it was also a controlled substance in Belarus, Denmark, Estonia, Finland, France, Germany, Hungary, Lithuania, Luxembourg, Malta, Poland, Portugal, Romania, Slovenia, Sweden, Turkey, China and the US state of Florida.

Although methiopropamine had been available online from UK-based Internet sites,[8] there are no published data available on the prevalence of use of methiopropamine from population or sub-population surveys in the UK or elsewhere. Its use in the UK had been confirmed by the detection in pooled street urinal samples in London from March 2012 until June 2017 and other UK cities in April 2014.[9-12] The UK National Programme on Substance Abuse Deaths (NPSAD) reported that methiopropamine was found in 16 post-mortem analyses in 2015, and thought to be implicated in the cause of death in 6 of these.[13] Methiopropamine was also reported in an Australian fatality in 2015.[14] There are limited published data on acute methiopropamine toxicity – there have been only two previous reports of patients with acute recreational drug toxicity where methiopropamine

was detected analytically.[15, 16] Here we describe a case series of eleven patients with analytically confirmed methiopropamine use.

Methods

The Identification Of Novel psychoActive substances (IONA) study is collecting and analysing biological samples from patients aged 16-years and older presenting to participating hospitals in the UK (26 sites as of June 2018) with pre-defined severe acute toxicity suspected to be due to NPS use [17]. These criteria include hyperpyrexia > 38.5^{o}C, Glasgow Coma Scale (GCS) < 8, requirement for endotracheal intubation and/or critical care admission, seizures, psychosis or severe prolonged behavioural disturbance, tachycardia > 140/min or arrhythmia, systolic blood pressure >180 or <80 mmHg, creatine kinase > 1000 IU/L, AST or ALT > 300 IU/L, hypoglycaemia, acute kidney injury, prothrombin time > 15 seconds, poisons severity score of 3 and any other severe manifestation suspected to be caused by exposure as determined and justified by the clinical team. Potential participants are identified by the clinicians managing them, who check that they meet these inclusion criteria and then obtain consent. Those unable to provide consent can be included on the advice of a personal (e.g. family member) or professional (e.g. health professional unconnected with the study) consultee, but consent is subsequently sought from the participant if and when they have recovered sufficiently.

Residual biological samples (blood, urine and/or saliva) taken for routine clinical management were analysed by liquid-chromatography High-Resolution Accurate-Mass tandem mass-spectrometry, as previously described in detail. [17] Briefly, we used data independent Sequential Window Acquisition of all Theoretical fragment-ion spectra (SWATH) mass spectrometry (SWATH MS Sciex, Framingham, MA). This utilises the very fast scanning speeds of QqTOF mass spectrometers and repeatedly cycles through consecutive pre-set precursor ion isolation windows, detecting all fragment ion spectra from all precursor ions contained in a specific window at a given time, providing highly selective MS/MS mass spectra of all analytes. To identify unknown compounds we processed LC-MS/MS data using MasterView software version 2.2. (Sciex, Framingham, MA), identifying compounds by software-assisted library searching against reference spectra using LibraryView version 1.0 (Sciex, Framingham, MA) and ChemSpider Library version 2.0 (Royal Society of Chemistry, Cambridge, UK).

The IONA study has ethical and research governance approval.[17] For this study, patients recruited to the IONA project where methiopropamine was detected were identified from the IONA database

and demographic, exposure details, clinical features and outcome data were extracted, as supplied by the treating clinicians.[17]

Case Series

There were 414 IONA patients recruited from the launch of the study on 22nd March 2015 for whom analytical data was available by 20th June 2018. One or more novel psychoactive substances were detected in at least one sample from 235 (57%) of these, conventional drugs of misuse were detected in 352 (85%) and no drug of misuse was detected in 14 (3%). Methiopropamine was detected in 11 (2.6%) patients, including 7 of 55 (12.7%) recruited during 2015 and 4 of 172 (2.3%) recruited during 2016. Methiopropamine was not detected in any of the 187 cases recruited between September 2016 and 10th May 2018. It was detected in blood (7 patients), urine (1 patient) and both blood and urine (2 patients). Median age was 24 (range 17-45) years; 9 (82%) patients were male. Cases were detected in London (4 patients), Liverpool (2), Newcastle (2), Blackpool (1), Edinburgh (1) and Manchester (1).

The demographics, self-reported drugs used, analytical findings, clinical features and outcomes are summarised in Table-1. Methiopropamine was the only substance detected in one patient; other drugs detected in the remaining 10 patients included other NPS or their metabolites in 9 and conventional drugs of misuse in 5 patients; synthetic cannabinoids were the most frequent NPS and most frequent class of drug overall detected alongside methiopropamine with seven different types detected. The most commonly reported clinical features were tachycardia, agitation, confusion, hallucinations, mydriasis and seizures. Five patients had a GCS less than 15, of whom three had had a seizure. The most common blood abnormalities were mildly raised transaminases in 5 patients (range 68-349IU/L); and raised creatine kinase activity in 7 patients (range 152-189,836IU/L). Of these, 4 had “rhabdomyolysis” (creatine kinase > 5x upper normal limit), all with a creatine kinase >1000IU/L and two of these had evidence of serotonin syndrome (hyperpyrexia ≥38^{o}C), hypertonia, agitation/severe confusion). Both required admission to an intensive care unit (level 3 bed) and intubation for management. Reported complications were acute kidney injury with a peak creatinine concentration of 1058mmol/L (patient 5) and pneumonia (patient 7). Patient 3 was the only patient to have methiopropamine and no other drugs of misuse detected analytically. He presented 87 minutes after smoking (no substance was reported). His only documented clinical feature was a tachycardia of 126 beats per minute, and he was discharged home after 2 hours.

All patients survived to discharge from hospital with a median length of hospital stay of 16.5 hours (range 2-185 hours, IQR 4-90 hours); ten were discharged home and one was transferred for ongoing psychiatric treatment. The seven patients with a raised creatine kinase required a longer length of stay (median (IQR) 40 (7-138) hours, range 4-185 hours) compared to those who did not have a raised creatine kinase (median (IQR) 10 (3-17) hours, range 2-17 hours). Two patients had a persistently raised creatine kinase and two had a persisting tachycardia at the time of discharge from hospital.

Discussion

We report the detection of methiopropamine in eleven (2.6%) of 414 patients with severe acute recreational drug toxicity suspected to be due to the use of NPS. The clinical features seen in this series were predominately sympathomimetic in nature. This is similar to the two previous case reports where methiopropamine was detected.[15, 16] The first reported case was in London, UK in 2014 where a 27 year old woman presented 21hours after oral ingestion of "Hawaiian baby seeds" and nasal insufflation of "Quicksilver" powder with insomnia, intermittent palpitations, chest tightness, nausea and vomiting, dizziness, anxiety, euphoria, visual hallucinations, agitation and mydriasis; urine screening detected methiopropamine (400ug/mL) along with morphine, erginovine and metabolites of the synthetic cannabinoids JWH-018 and JWH-019.[16] The other case was in 2016 where a 30year old man presented after smoking cannabis and ingested "synthacaine" with confusion, paranoid delusions, auditory and visual hallucinatory experiences and incoherent speech; the initial urinary immunoassay screening was positive for cannabinoids only. However toxicological analysis using LC-MS/MS detected only methiopropamine (plasma 14ng/mL; urine 8,160ng/mL).[15]

All of the cases in which methiopropamine was detected in this series occurred prior to August-2016, with 8 before and 3 after methiopropamine was subject to a Temporary Class Drug Order in November 2015. No further cases have been detected in the IONA study since methiopropamine became controlled as a Class-B substance. [7] It is unclear as to whether legislation has had an impact on the frequency of detection of use of methiopropamine in patients presenting to hospital with acute toxicity, or whether its popularity has decreased as the variety of NPS available has increased.[18] None of the patients in our series in whom methiopropamine was detected had self-reported the use of methiopropamine, although seven did report the use of an NPS. In the two previous case reports neither patient reported use of methiopropamine, although both reported use of an NPS.[15, 16] Previous studies have demonstrated that there is variation in the contents of

NPS,[19-22] and it is possible that patients had inadvertently used an NPS or established drug that they were unaware contained methiopropamine. The clinical effects seen in this series are consistent with sympathomimetic exposure, although a limiting factor in this study is that co-used substances are likely to have contributed to these effects. Patient 11 only had methiopropamine detected in his urine, not his blood, suggesting that despite exposure to methiopropamine, his presentation with acute intoxication may not have been due to acute methiopropamine use. Another limitation of this study was that we did not have the resources to quantify the amount of methiopropamine detected in our biological samples. This study demonstrates the value of the IONA project in confirming the NPS involved in severe acute recreational drug toxicity presentations to the emergency department to determine trends in the NPS involved and consider the impact of legislative changes. It is likely that methiopropamine causes a sympathomimetic picture with a raised creatine kinase, although its frequent detection with co-used substances makes this hard to confirm.

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Table 1: The demographics, self-reported drugs used, analytical findings, clinical features, blood results and outcomes. All patients had methiopropamine analytically detected.

Patient		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Age (years)		19	24	43	22	23	21	33	45	34	17	29
Gender		F	M	M	M	M	F	M	M	M	M	M
Substances Reported Used *(NR = not reported)*		New cannabis, LSD, Mushroom tea	Poppers, Dusk till dawn	NR	NR	Vertex	Octagon, Ecstasy, Cocaine	Pandora reborn	Legal high	Black chronic	Party pills, cannabis	Street drug
Positive Methiopropamine Biological Specimens Tested		Blood & urine	Urine (no blood specimen received)	Serum	Serum	Plasma	Plasma	Plasma	Whole blood	Serum	Plasma	Urine (not detected in plasma)
Other NPS Detected		5F-PB-22, FUB-NPB-22, Omberacetam	FUB-PB-22, 5F-AKB-48	None	25I-N-BOMe, STS-135	MDMB-CHMICA	2AI, AM-1248	3F-Phenmetrazine	Ethylphenidate, Methylmethylphenidate	5F-ADB, 2-AI, etizolam, 3-fluorophenmetrazine	None	Omberacetam
Classical Drugs Detected		Citalopram, Diazepam	Mirtazepine, Diazepam, Temazepam, Oxazepam, Paracetamol	None	None	None	Methadone	Methadone, Benzocaine	Diazepam, Citalopram	Methadone, Diazepam, Norclobazam, MDMA	MDMA, Methadone	Methamphetamine, Gabapentin, paracetamol, quinine
Clinical Features (Y = yes, N = no, NR = not reported)	Hyperpyrexia (T $\geq$ 38^{o}C)	N	N	N	N	38.0	N	38.6	N	N	N	N
	GCS (< 15)	9	N	N	N	N	3	13	N	9	N	14
	Seizure	Y	N	N	N	N	Y	N	N	Y	Y	N
	Mydraisis	Y	Y	N	N	Y	Y	N	N	N	Y	N
	Hypertonia	Y	N	N	N	Y	N	Y	N	N	N	N
	Hyperreflexia	Y	N	N	N	N	N	Y	N	N	N	N
	Clonus	Y	N	N	N	N	N	NR	N	N	N	N
	Dystonia	N	N	N	N	Y	N	NR	N	N	N	N
	Tachycardia (BPM $\geq$ 100)	120	135	126	125	N	130	130	111	101	127	140
	Hypertension (SBP $\geq$ 160)	185	160	N	N	N	N	167	N	N	N	N
	Dizziness	Y	Y	N	N	Y	N	N	N	N	N	Y
	Palpitations	N	Y	N	N	N	N	Y	Y	N	N	N
	Breathing difficulties	N	Y	N	N	N	N	Y	N	N	N	N
	Agitation	N	Y	N	NR	Y	Y	Y	N	Y	Y	Y
	Aggression	N	N	N	NR	N	Y	Y	N	Y	N	Y
	Confusion	Y	N	N	NR	Y	Y	Y	N	Y	Y	Y
	Hallucinations	Y	N	N	NR	Y	Y	N	N	Y	N	Y
	Paranoid Ideation	N	N	N	NR	Y	Y	N	N	N	N	Y
	Other	NR	Bleeding	NR	NR	Bleeding	N	Sweating	Chest pain	N	N	Headache
Peak Blood results	Acidosis (pH <7.35)	7.25	N	N	N	N	N	N	N	N	7.06	N
	Lactic acidosis (lactate > 2mmol/L)	N	5.8	N	N	NR	NR	NR	N	N	19.4	NR
	Raised creatinine (> 85umol/L)	N	N	N	NR	1058	N	N	N	N	N	N
	Raised transaminases	N	N	N	NR	79	170	95	N	68	349	N
	Raised CK (>159 IU/L)	152	277	N	358	14687	70355	1715	N	305	189836	NR
	Prothrombin time (>13.2 seconds)	NR	N	N	NR	15	N	17	N	NR	15	N
	Raised Urea (>8.3mmol/L)	NR	NR	NR	NR	15.3	NR	11.9	N	NR	NR	NR
	MetHb (%)	NR	37.6	NR	NR	NR	NR	NR	N	NR	NR	NR

	Hyponatraemia (<135mmol/L)	NR	NR	NR	NR	NR	NR	NR	N	NR	126	NR
	WBC (>11.0x10^9)	NR	NR	NR	NR	28	NR	24	N	NR	NR	NR
	CRP (>5mg/L)	NR	NR	NR	NR	NR	NR	116	N	NR	NR	NR
Treatment	Intubation and Ventilation	N	N	N	N	Y	N	Y	N	N	N	NR
	Cooling	N	N	N	N	N	N	Y*	N	N	N	NR
	Other (see below)	N	**	N	N	N	***	****	N	N	N	NR
Overall Length of Stay (hours)		17	7	2	4	185	138	90	3	16	40	18
Discharge outcome	**Home**	y		Y	Y	Y	Y	Y	Y	Y	Y	Y
	Psychiatry Inpatient		Y									

*External cooling by fan **Treatment with methylene blue *** Treatment with IV sodium bicarbonate **** Sedation